

Claims

What is claimed is:

5. 1. A pharmaceutical composition comprising an acetylcholinesterase inhibitor and an inverse agonist of the GABA_A $\alpha 1$ and/or $\alpha 5$ receptor subtype wherein the inverse agonist has a functional efficacy at the $\alpha 1$ and/or $\alpha 5$ receptor subtypes of less than -5%, preferably less than -10%, and the efficacy measured at the $\alpha 2$ and $\alpha 3$ receptor subtypes is greater than 5% or preferably greater than 10%, and a pharmaceutically acceptable carrier, said composition being effective in the treatment
10 of a cognitive disorder.

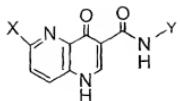
15. 2. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional potency (EC50 values) at the $\alpha 1$ and/or $\alpha 5$ receptor subtypes of 200 nM, preferably less than 150 nM.

15. 3. The pharmaceutical composition of claim 1, wherein the inverse agonist has a functional efficacy at the $\alpha 5$ receptor subtype of less than -5%, preferably less than -10%, and the efficacy measured at the $\alpha 1$, $\alpha 2$ and $\alpha 3$ receptor subtypes is greater than 5% or preferably greater than 10%.

20. 4. The pharmaceutical composition of claim 3, wherein the inverse agonist has a functional potency (EC50 values) at the $\alpha 5$ receptor subtype of 200 nM, preferably less than 150 nM.

25. 5. The pharmaceutical composition of claim 1, wherein the inverse agonist at the $\alpha 1$ and/or $\alpha 5$ receptor subtypes has a binding Ki of 100 nM, preferably less than 30 nM.

30. 6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a GABA_A inverse agonist, and an acetylcholinesterase inhibitor, wherein said GABA_A inverse agonist is selected from a compound of Formula I below:



I

wherein:

5 X is hydrogen, halogen, -OR₁, NR₂R₃, C₁-C₆ alkyl optionally substituted with up to three groups selected independently from halogen and hydroxy, or -NR₂R₃; or

10 X is phenyl, naphthyl, 1-(5,6,7,8-tetrahydro)naphthyl or 4-(1,2-dihydro)indenyl, pyridinyl, pyrimidyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzothienyl, each of which is optionally substituted with up to three groups selected from halogen, C₁-C₆ alkyl, C₁-C₄ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆) alkylamino, cyano, nitro, trifluoromethyl; or

15 X represents a carbocyclic group ("the X carbocyclic group") containing from 3 – 7 members, up to two of which members are optionally hetero atoms selected from oxygen and nitrogen, where the X carbocyclic group is optionally substituted with one or more groups selected from halogen, (C₁-C₆)alkoxy, mono- or di(C₁-C₆)alkylamino, sulfonamide, aza(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkylthio, (C₁-C₆)alkylthio, phenylthio, or a heterocyclic group; and

20 Y is lower alkyl having 1 – 8 carbon atoms optionally substituted with up to two groups selected from halogen, (C₁-C₆)alkoxy, mono- or di(C₁-C₆)alkylamino, sulfonamide, aza(C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkylthio, (C₁-C₆)alkylthio, phenylthio, a heterocyclic group, -OR₄, -NR₅R₆, SR₇, or aryl; or

25 Y is a carbocyclic group ("the Y carbocyclic group") having from 3 – 7 members atoms, where up to three of which members are optionally hetero atoms selected from oxygen and nitrogen and where any member of the Y carbocyclic group is optionally substituted with halogen, -OR₄, -NR₅R₆, SR₇, aryl or a heterocyclic group; and

30 R₁ is hydrogen, lower alkyl having 1 – 6 carbon atoms, or cycloalkyl having 3 – 7 carbon atoms, where each alkyl may be optionally substituted with -OR₄ or -NR₅R₆;

35 R₂ and R₃ are the same or different and represent hydrogen, lower alkyl optionally mono- or disubstituted with alkyl, aryl, halogen, or mono- or di-lower alkyl;

aryl or aryl (C_1 - C_6)alkyl where each aryl is optionally substituted with up to three groups selected from halogen, hydroxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, or mono- or di- (C_1 - C_6)alkylamino;

cycloalkyl having 3 – 7 carbon atoms optionally mono or disubstituted with

5 halogen, alkoxy, or mono- or di- lower alkyl; or

$$-\text{SO}_2\text{R}_8;$$

R_4 is as defined for R_1 ;

R_5 and R_6 carry the same definitions as R_2 and R_3 , respectively;

R₇ is hydrogen, lower alkyl having 1 – 6 carbon atoms, or cycloalkyl having

10 3–7 atoms; and

R_8 is lower alkyl having 1 – 6 carbon atoms, cycloalkyl having 3 – 7 carbon atoms, or optionally substituted phenyl.

or a pharmaceutically acceptable prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

15 said composition being effective in the treatment of a cognitive disorder.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, a GABA_A inverse agonist, and an acetylcholinesterase inhibitor, wherein the GABA_A inverse agonist is selected from the group consisting of:

20 **N-n-Butyl-6-chloro-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide:**

N-n-Butyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide:

N-(2-Ethylthio)ethyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-n-Pentyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide:

N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide

N-(2-Tetrahydrofuryl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide:

N-Isoamyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide:

N-(3-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthoquinone carboxamide:

N-(3-Ethoxy)propyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-

N-(2-(2-Methyl)butyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-methyluridine-2-

11.2 (2-Methylbutyl 3-Ethoxy-1,1-tetrahydro-1,3-haptoxyphthalimide)

carboxamide;

5 N-5-Pentanol-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-Benzyl-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

10 N-(2-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Fluorobenzyl)-6-methoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

15 N-(4/5-Imidazolyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Thienyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Tetrahydropyranyl)methyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

20 N-(2-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-5-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

25 N-(4-Fluorobenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Methoxybenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Methylbenzyl)-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

30 N-(2-Thienyl)methyl-6-(2-methoxyethoxy)-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-morpholino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(2-Thienyl)methyl-6-dimethylamino-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(4-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide;

N-(3-Methylaminomethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide hydrochloride;

N-[4-(Imidazolylmethyl)benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide,

5 a pharmaceutically acceptable prodrug thereof, and a pharmaceutically acceptable salt or solvate of said compound or prodrug,

said composition being effective in the treatment of a cognitive disorder.

8. The pharmaceutical composition of claim 7, wherein the GABA_A 10 inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

9. The pharmaceutical composition of claim 7, wherein the 15 acetylcholinesterase inhibitor is selected from the group consisting of Aricept (donepezil, E2020), Exelon (rivastigmine), metrifonate, galantamine, physostigmine, tacrine, huperzine A, and icopezil, a prodrug thereof, and a pharmaceutically acceptable salt or solvate of said compound or prodrug.

20 10. The pharmaceutical composition of claim 9, wherein the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

11. The pharmaceutical composition of claim 7, wherein the GABA_A 25 inverse agonist is N-Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

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12. A method for treating a cognitive disorder in a mammal, comprising administering to a mammal in need of such treatment an effective amount of a combination of a GABA_A inverse agonist and an acetylcholinesterase inhibitor,

wherein the GABA_A inverse agonist and the acetylcholinesterase inhibitor are as defined in claim 1.

13. The method of claim 12, wherein the GABA_A inverse agonist is N-
5 Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

14. The method of claim 12, wherein the acetylcholinesterase inhibitor is
10 selected from the group consisting of Aricept (donepezil, E2020), Exelon (rivastigmine), metrifonate, galantamine, physostigmine, tacrine, huperzine A, and icopezil, a prodrug thereof, and a pharmaceutically acceptable salt or solvate of said compound or prodrug.

15. 15. The method of claim 12, wherein the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

16. The method of claim 12, wherein the GABA_A inverse agonist is N-
20 Benzyl-6-ethoxy-4-oxo-1,4-tetrahydro-1,5-naphthyridine-3-carboxamide, or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug; and the acetylcholinesterase inhibitor is Aricept (donepezil, E2020) or a prodrug thereof, or a pharmaceutically acceptable salt or solvate of said compound or prodrug.

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17. The method of claim 12, wherein the GABA_A inverse agonist and the acetylcholinesterase inhibitor are administered separately.

18. The method of claim 12, wherein the GABA_A inverse agonist and the
30 acetylcholinesterase inhibitor are administered sequentially.

19. The method of claim 12, wherein the GABA_A inverse agonist and the acetylcholinesterase inhibitor are administered simultaneously..

20. The method of claim 12, wherein the cognitive disorder is selected from the group consisting of Alzheimer's disease, mild cognitive impairment, age-related cognitive decline, vascular dementia, Parkinson's disease, memory impairment associated with depression or anxiety, psychosis, Down's Syndrome, 5 stroke, traumatic brain injury, and attention deficit disorder.

21. The method of claim 20, wherein the cognitive disorder is Alzheimer's Disease.

10 22. The method of claim 20, wherein the cognitive disorder is mild cognitive impairment.

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